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Vaccine risks: real, perceived and unknown ☆

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Abstract

As immunizations successfully reduce the incidence of their target diseases, the vaccine community needs to evolve and recognize the increased relative prominence of vaccine safety. Just as the aviation community maintained public confidence by its continuous investment in a safety infrastructure as it evolved from propeller to jet and jumbo planes, modernization of the vaccine safety infrastructure commensurate with the current investment in vaccine development will be needed if the full promise of new vaccines made possible by the biotechnology revolution are to be fulfilled. Published by Elsevier Science Ltd.

1. Introduction

Immunizations are among the most cost-effective and widely used public health interventions [1]. Biotechnology offers great promise in adding even more societal value via vaccinations [2]. No vaccine is perfectly safe or effective, however. As the incidence of vaccine-preventable diseases is reduced by increasing coverage with an efficacious vaccine, vaccine adverse events, both those caused by vaccines (i.e. true adverse reactions) and those associated with vaccination only by coincidence, become increasingly frequent (Fig. 1). The number of both types of reports to the Vaccine Adverse Event Reporting System (VAERS) in the United States [3], approximately 11,000/year, now exceeds the reported incidence of most vaccine-preventable childhood diseases combined (Table 1).

Not surprisingly, vaccine safety concerns have become increasingly prominent in such 'mature' immunization programs. Chronic illnesses recently claimed to be linked with vaccinations range from asthma [4], autism [5], diabetes [6], to multiple sclerosis [7]. Given the current increasingly 'anti-vaccine' milieu, it is hard to imagine that the full potential of new vaccines will be harnessed. To avoid this impending tragedy, we need to critically examine the factors influencing this change in public sentiments. Clearly, increasingly well organized consumer groups, the popularity of alternative health care, increasing competition in the news media and new rapid communication technologies have all contributed. But there are several factors directly related to the vaccine community, due either to our action or inaction, that may have contributed to the current unsatisfactory situation.

2. Evolutionary/dynamic nature of immunizations and risks of failure to adapt

In 1971, the US stopped routine smallpox vaccinations prior to global smallpox eradication due to the burden of vaccine-associated encephalopathy [8]. This experience, plus the concerns about the safety of whole cell pertussis vaccine in several countries that erupted 20 years ago [9], should have alerted us to the dynamic and evolutionary nature of balancing the risks and benefits of immunizations (Fig. 1). As with all evolutionary processes, there is great risk in failing to adapt.

Smallpox aside, polio is the only other vaccine-preventable disease likely to be eradicated globally in the

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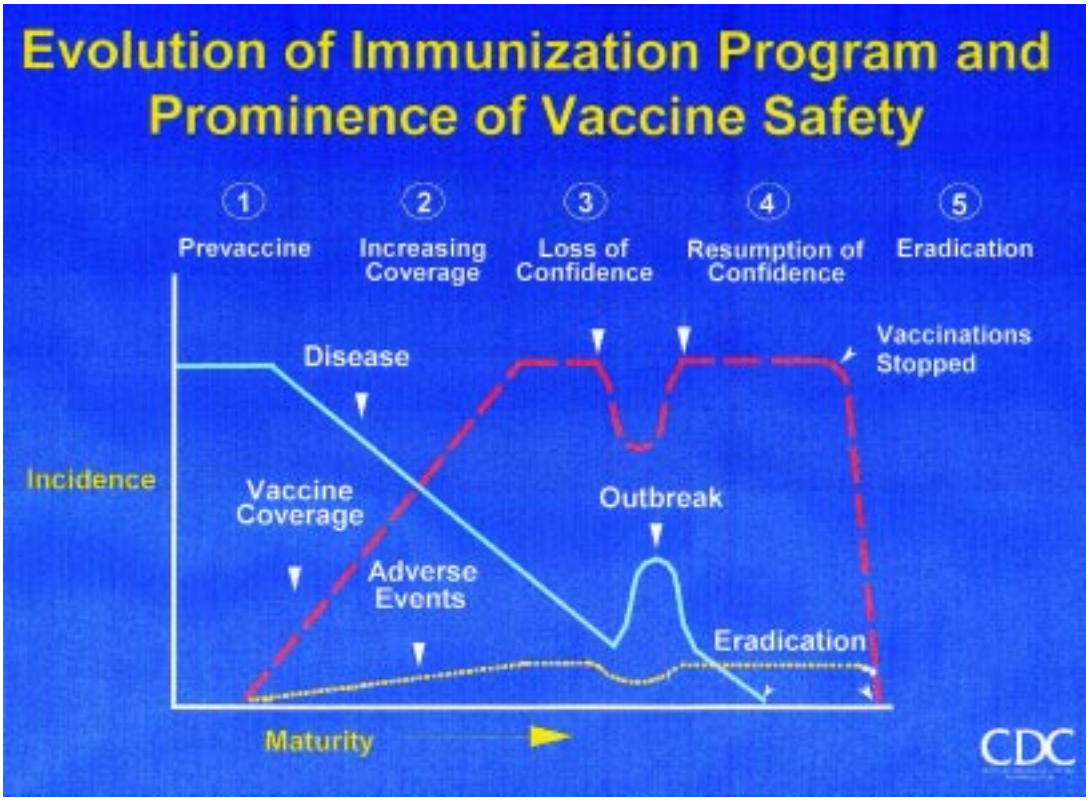

Fig. 1. Potential stages in the evolution of immunization program, showing the dynamics of the interaction between vaccine coverage, disease incidence and vaccine adverse events, as the program matures from pre-vaccine to disease eradication.

near future [10]. All the other immunizations will therefore be needed indefinitely. This places the managers of most 'mature' immunization programs in the uncomfortable position of high vaccine coverage and high incidence of vaccine adverse events relative to vaccine-preventable diseases, awaiting the next media scare and loss of public confidence (Fig. 1, stage 3). If a vaccine needs to be used indefinitely, the only way forward is to better understand which vaccine adverse events are true reactions. And if true, what is the attributable risk so that it can be communicated to the public and policy makers accurately [11–13], identify risk factors that may permit development of valid contra-indications [11,14] and if the pathophysiology

Table 1
Comparison of maximum and current reported morbidity vaccine preventable diseases and vaccine adverse events, United States, 1998

Disease	Maximum cases (yr)	1998[a]	Percentage change
Diphtheria	206,939 (1921)	1	−99.99
Measles	894,134 (1941)	89	−99.99
Mumps	152,209 (1968)	606	−99.60
Pertussis	265,269 (1934)	6279	−97.63
Polio (wild)	21,269 (1952)	0	−100.00
Rubella	57,686 (1969)	345	−99.40
Cong. Rubella synd.	20,000[b] (1964–5)	6	−99.98
Tetanus	1560[b] (1948)	34	−97.82
Invasive *Hib* disease	20,000[b] (1984)	51	−99.75
Total	1,639,066	7411	−99.55
Vaccine adverse events[c]	0[b]	(10,236)	

[a] Final totals of reported cases to the CDC.
[b] Estimated because no national reporting existed in the prevaccine era.
[c] Total reports of adverse event after vaccination against the diseases listed = 5.522.

mechanism becomes known, develop safer vaccines [15,16].

3. Recognition of importance of vaccine safety: safety first vs. safety last

In this evolutionary process, we have been relatively slow in appreciating the importance that the public now places on vaccine safety. In fact, much of our resource allocations still unfortunately reflect safety last rather than safety first. This reflects in part an unfortunate legacy of us characterizing this arena for years in narrow, negative terms of *adverse events*, instead of the more broad and positive terms of *safety*. Furthermore, it shows that we have not been as interested in preventing vaccine-induced illnesses as we are with vaccine-preventable diseases.

In contrast to most pharmaceutical products, which are administered to ill persons for curative purposes, vaccines are generally given to healthy persons to prevent disease. As an extension of the medical maxim 'first do no harm,' tolerance of adverse reactions to products given to healthy persons — especially healthy infants — is substantially lower than to products administered to persons who are already sick. This lower risk tolerance for vaccines translate into a need to investigate the possible causes of much rarer adverse events following vaccinations than would be acceptable for other pharmaceutical products. For example, events occurring at $\sim 1/10^5$–$1/10^6$ doses like acute encephalopathy after whole cell pertussis vaccine [11,17], Guillain–Barre syndrome (GBS) after swine influenza vaccine [18] and oral polio vaccine-associated paralytic polio (VAPP) [10] are of concern for vaccines while side effects are essentially universal for cancer chemotherapy and 10–30% for persons on high dose aspirin therapy experience gastro-intestinal symptoms [19].

The cost and the difficulty of studying events increase with their rarity, however. Furthermore, the ability to provide definitive conclusions from epidemiologic studies of rare events decreases. Attributable risks on the order of $1/10^5$–$1/10^6$ are on the margin of resolution for epidemiologic methods [17,20]. Perhaps not surprisingly, the bulk of the published literature on vaccine safety to date has been in the form of case reports and case series rather than controlled studies with adequate power [17,21].

4. The need for better data on vaccine risks

In this new 'vaccine safety'-conscious environment, there is a critical need for better data on rare vaccine risks. We know that the sample size of even the largest pre-licensure trials, in the low thousand or tens of thousands, are calculated primarily based on efficacy rather than safety considerations [22]. While such trials have advantages in their ability to assess causality of vaccine adverse events due to their experimental design, they are limited their ability to provide data on rare, delayed, or reactions in subpopulations. Furthermore, the lack of standardization of case definitions for various adverse events (e.g. fever, fussiness) in such trials limit our ability to interpret and use these 'safety' data.

Table 2
Public perceptions of risk based on risk characteristics[a] (Italic = vaccination)

Less risk		Greater risk
voluntary	vs.	*involuntary*
individual control	vs.	*system control*
omission	vs.	*commission*
natural	vs.	*manmade*
not memorable	vs.	*memorable*
knowable	vs.	unknowable
not dreaded	vs.	dreaded
trustworthy	vs.	untrustworthy
familiar	vs.	*exotic*

[a] Adapted from Hance 1990 [25].

Due to these limitations, the 'mantra' has been to rely on post-marketing surveillance to detect rare serious problems. Yet this has been more an aspiration than reality. For example, the World Health Organization's Expanded Programme on Immunizations (EPI) recommended in 1991 for all national programs to establish surveillance for adverse events following immunizations [23]. As of 1997, however, only 12 (14%) of 88 national EPI's had such a system in place. Without such surveillance, it is clearly difficult to make the best evidence-based decisions [24].

Similarly, current knowledge and research capability about rare vaccine risks is incomplete and limited, as noted in extensive reviews in early 1990's by the Institute of Medicine (IOM) in the United States [17,21]. Two-third of the 76 vaccine adverse events evaluated by the IOM were found to have either no or inadequate evidence to assess for or against a vaccine cause. Specifically, the Committee identified the following limitations: (1) inadequate understanding of biologic mechanisms underlying adverse events; (2) insufficient or inconsistent information from case reports and case series; (3) inadequate size or length of follow-up of many population-based epidemiologic studies; (4) limitations of existing surveillance systems to provide persuasive evidence of causation; (5) few experimental studies published relative to the total number of epidemiologic studies published.

Another area worthy of more research is vaccine

Table 3
Aviation and vaccine safety analogies

Aviation	Vaccines
Airbus/Boeing	PMC, SKB, MSD, etc.
Radar/Air Traffic Control	Disease and adverse event surveillance
Global positioning system	PCR
Frequent flyer programs	Immunization registries
Jumbo jets	Mass campaigns
Concorde	DNA vaccines
Airlines	National immunization programs
Federal Aviation Administration	Food and Drug Administration
Airport excise tax	Vaccine excise tax
National Transportation Safety Board	?

risk communications [25]. The vaccine risk-benefit literature equates cases of morbidity and mortality, irrespective of whether they are caused by wild disease or by vaccine. Research in risk communications suggest, however, that public perceptions of risk vary dramatically depending on the characteristics of the risk (Table 2) [25]. Unfortunately for vaccine, most of its characteristics tend to be those that the public may perceive to be at greater risk [26]. This may explain, in part, the vulnerability of immunization programs to vaccine safety scares [9].

5. How to prevent creating anti-vaccine activists?

Most persons are not born 'anti-vaccine'. There remains much that we can do to prevent their creation which we have yet to do. For example, in countries where immunizations are mandated, increasing the availability of philosophical exemptions may provide a 'relief valve' [27]. In such situations, close monitoring the risk of vaccine-preventable disease in unimmunized exempters and their subsequent transmission to the larger community may help dissuade others [28]. Improved vaccine risk communications, especially via a shift from traditional paternalistic to a shared decision making model, can help produce more informed consumers. We should also substitute the 'one size fits all' approach to producing vaccine educational material with at least two-tiers: a simple one for the great majority and a detailed one with all the scientific references for the increasingly sophisticated consumer.

Should a person be unfortunate to experience and report a vaccine adverse event, we should try to ensure that he or she receives a personalized follow-up. During such subsequent contact, more details on the adverse event can be systematically gathered, status current knowledge and research (lack of) regarding the causal relation between the vaccine and the event can be conveyed and any questions that the patient might have answered. Doing so will help to convey a sense that the 'system' is concerned about the negative experiences of a consumer of immunization services — at least more so than a form letter.

There is probably also a 'missed opportunity' to better understand vaccinology by not enhancing our use of reports to systems like VAERS in either clinical research or as a 'registry' of potential rare serious vaccine reactions. Much science is advanced by study of the 'exceptions' to the rule. For example, the genetic basis for hepatitis B vaccine failure has recently been elucidated [29]. Preliminary work also suggests there might be a genetic basis for the link between hepatititis vaccination and rheumatoid arthritis [30]. Such research may be conducted in regional 'special immunization clinics', where persons who have had prior adverse events can be immunized under close observation and follow-up, thereby permitting other special vaccine safety research under protocol [31]. Finally, nothing may prevent creation of anti-vaccine activists more than ensuring that there is adequate funding for vaccine safety infrastructure and research.

6. Need for investment in vaccine safety infrastructure (commensurate with vaccine development)

If we are truly serious about fulfilling our potential in new vaccine development, we have to be equally willing to invest in improving the vaccine safety infrastructure. An useful, if imperfect, analogy may be to compare the vaccine and the aviation community (Table 3). Imagine how difficult it must have been to convince the average person back in the 1920's and the 1930's that flying was safe. Most of us fly so frequently now that we don't even think about it. Yet would we do so, if we did not know that there was a sophisticated aviation safety infrastructure of radars and air traffic control in place? Slowly over the years, via a collaboration between the private and public sectors in the US and Europe, an aviation safety infrastructure has been built to provide the necessary public confi-

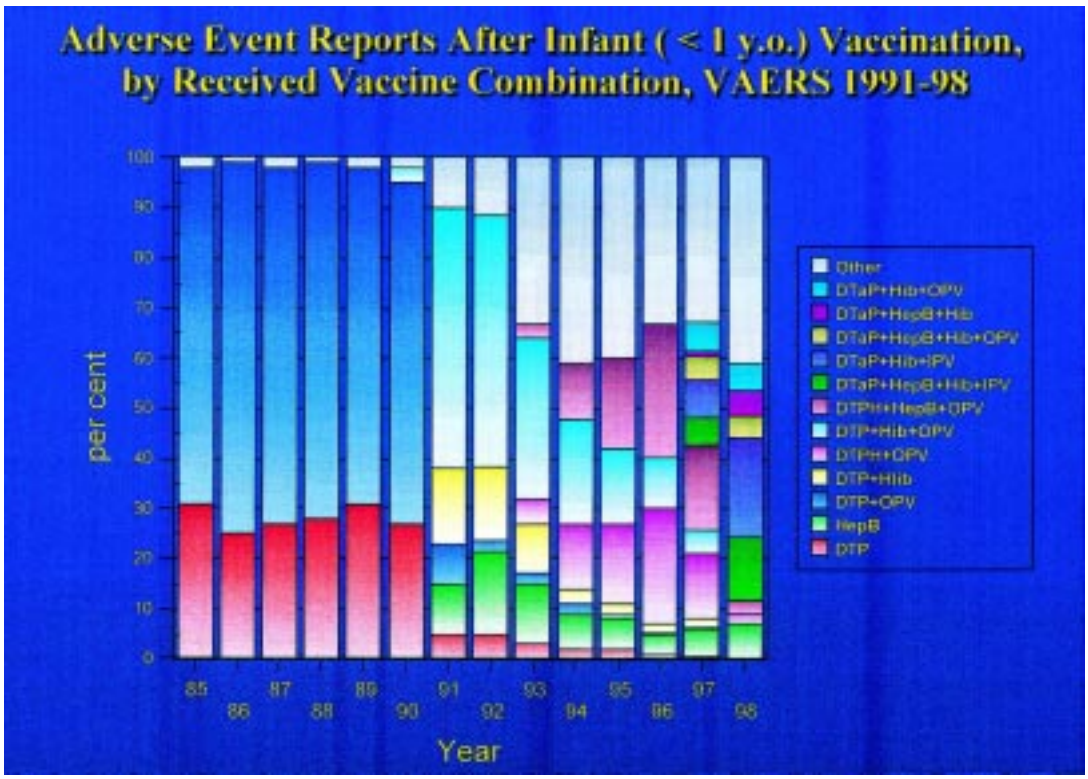

Fig. 2. Adverse event reports after infant vaccinations by reported vaccine combinations received, United States, 1985–98, illustrating the increasing complexity of the routine infant immunization schedule.

dence in flying. Equally important, as planes developed from propellers to jets, then jumbo jets and Concorde, the technology for improving aviation safety also evolved. Yes, in the event of an unfortunate crash, millions may have flown without difficulties, yet a careful investigation is still launched immediately to better understand this specific exception to the rule. Whatever changes needed, be it hardware, software, or policy, can then be identified and improved via systematic feedback.

Applying this 'systems' analysis from aviation to vaccines, we immediately see several shortcomings. While much investment may have been made in the hardware and software in the vaccine development and vaccine production, much of the surveillance tools for vaccine safety remains relatively primitive. Important strides have been made in developing newer large-linked databases for active surveillance of vaccine safety [12,32]. Yet nowhere globally are such systems stably funded or fully operational. Imagine having radar to avoid plane crashes and not using them, or having them but without enough staff to monitor the radar screen. In aviation, the airport excise tax is not used to just to compensate those unfortunate to have perished in airplane crashes; it is used to improve the radar, the runways and all the infrastructure necessary to prevent such tragedies from occurring. In contrast, the US vaccine excise tax has been jealously guarded by certain interests for use for injury compensation only, but not for improving understanding of vaccine safety as intended by its sponsor, Senator Paula Hawkins: "Although compensation of the injured children is a key component of S. 2117, the other provisions of this bill are of equal importance, perhaps more important, because they are designed to improve the entire immunization program to prevent the injuries in the first place".

Finally, one institution critical to the system of aviation safety is missing in the vaccine arena: the National Transportation Safety Board (NTSB). This small, non-regulatory, independent and highly respected agency seeks to proactively prevent and/or reduce the severity of future accidents. It provides independent oversight of the transportation system by monitoring the effectiveness of regulatory bodies at various government levels. The NTSB seeks to gain public trust by its independence, objectivity, technical competence and proactive stance on prevention. By partnering with industry and other government entities during its investigations, the NTSB not only works efficiently but also gains consensus on its recommendations. As the immunization schedule grows increasing complex (Fig. 2), the vaccine community may best increase the likelihood of adding more societal value via vaccinations, by creating National Immunization Safety Boards [33].

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